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TOWNSEND and TOWNSEND and CREW LLP

By: _____

PATENT
Attorney Docket No. 019904-002610US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5231
Joseph K. Belanoff	Examiner: Donna A. Jagoe
Application No.: 10/772,919	Technology Center/Art Unit: 1614
Filed: February 4, 2004	APPELLANTS' REPLY BRIEF UNDER 37 CFR §41.41
For: ANTIGLUCOCORTICOIDS FOR THE TREATMENT OF POSTPARTUM PSYCHOSIS	

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Further to the Appeal Brief mailed on October 28, 2009, and in response to the Examiner's Answer mailed on January 25, 2010 for the above-referenced application, Appellants submit this Reply Brief. A request for Oral Hearing accompanies this paper.

No additional fees are believed to be necessary. If however, any additional fees are required, I authorize the Commissioner to charge these fees which may be required to Deposit Account Number 20-1430.

REPLY BRIEF

The present Reply Brief is filed to address new issues raised in the Examiner's Answer mailed January 25, 2010. No new amendments, affidavits, or evidence are included. A copy of the claims is included for reference as a Claims Appendix.

ARGUMENTS

The following acronyms are used in this section:

GR:	glucocorticoid receptor
GRA:	glucocorticoid receptor antagonist
PPP:	postpartum psychosis
PPD:	postpartum depression
PMD:	psychotic major depression
DSM IV:	Diagnostic and Statistical Manual of Mental Disorders IV (2000)
IUPAC:	International Union of Pure and Applied Chemistry

A. GROUND OF REJECTION 1 (Claims 1-11 and 15): 35 USC § 103

The issue on appeal remains the same; Appellants maintain that the Examiner has applied an improper standard for obviousness. Instead of explaining why one of skill would have a reasonable expectation of success in treating PPP with a GRA, the Examiner has shifted the burden of proof, and asserted that, absent evidence from the prior art that PPP is **NOT** amenable to treatment with a GRA, it will be viewed as such. Appellant arguments on this issue are of record, as is evidence teaching away from treating PPP with a GRA.

Appellants address each new argument raised in the Examiner's Answer in turn below.

1. The disclosure of PPP in the Detailed Description section is not controlling

Appellants maintain that the Examiner's interpretation of Schatzberg, the cited reference, is wrong. Schatzberg discloses PPP under the definition for psychosis, a section that broadly describes psychosis in general. Appellants urge that one of skill would understand this as background information about psychosis, not necessarily included in the invention of treating

certain types of psychosis with a GRA. The introductory sentence of Schatzberg limits the invention to treating psychoses *related to glucocorticoid regulatory dysfunction.*

In yet another attempt to justify reading the definition of psychosis into the invention of Schatzberg, the Examiner states that the words "postpartum psychosis" appear in the Detailed Description of the Invention section of Schatzberg, instead of the Background of the Invention (Examiner's Answer, pages 15-16). The Examiner cites 37 CFR 1.71 and MPEP 608.01 to argue for the first time that all information disclosed in the Detailed Description of the Invention is included in the invention.

The Examiner is wrong. Rule 71 sets forth positive requirements for the specification, but does not state that every disclosure in the Detailed Description section is included in the invention. Essentially, the rule states that the specification must comply with 35 USC § 112, so that it sufficiently describes and enables the invention. To this end, the specification of Schatzberg provides a broad definition for psychosis, and states that the invention relates to those types of psychosis that are related to glucocorticoid regulatory dysfunction. Appellants are unaware of any law, rule, or guidance stating that every word in the Detailed Description section is part of the invention.

Moreover, the Examiner has taken a position that is internally inconsistent. In contrast to PPP, Appellants and the Examiner would appear to be in agreement that Schatzberg specifically excludes schizophrenia and manic states from the invention. Yet these terms are also disclosed in the Detailed Description of the Invention. The Examiner makes no attempt to reconcile this discrepancy in logic.

Appellants take this opportunity to reiterate that Schatzberg repeatedly states that the invention relates to GRA treatment of psychoses resulting from glucocorticoid regulatory dysfunction. While Schatzberg defines "psychotic" in its broadest sense, it does not suggest that all psychoses are related to glucocorticoid regulatory dysfunction.

Rule 71 is inadequate to support the Examiner's burden of supporting a reasonable expectation that PPP is related to glucocorticoid regulatory dysfunction. Mere inclusion of PPP in a definition is not sufficient for the Examiner's point.

2. Stowe is not relevant to the presently claimed invention

Appellants have questioned the continued relevance of Stowe to the *prima facie* case of obviousness. Stowe, a reference initially cited by the first examiner, Examiner Packard, to link postpartum depression (PPD) with psychotic major depression (PMD) (*see* Office Action mailed December 20, 2007, pages 3-4). PMD is the focus of Schatzberg, the primary reference, and PPD is the focus of Stowe. In the Response mailed February 13, 2008, Appellants distinguished PPP from PPD, and submitted exhibits in support of this point.

The second examiner, Examiner Jagoe, apparently ignoring these references, continues to rely on Stowe. The Examiner states on page 18 of the Examiner's Answer that "Stowe is employed to show the postpartum patient population may include those without predisposed depression tendencies," citing to "the response dated May 19, 2009 and the office action dated May 28, 2008." The Examiner continues, stating that one cannot show nonobviousness by attacking references individually where the rejection is based on combinations of references.

First, Appellants *have never argued* that the postpartum patient population includes only those individuals with predisposed depression tendencies. Indeed, the Response mailed February 13, 2008 argued that PPP is distinct from PPD (which may or may not include individuals with predisposed depression tendencies). Predisposition to depression tendencies is not at issue, thus, Stowe is not relevant to the present *prima facie* case of obviousness.

Secondly, it appears that the present Examiner has re-raised Stowe despite the fact that the reference was overcome with the first examiner, Examiner Packard. Pages 5-6 of the Response mailed July 11, 2008, indicate that Examiner Packard acknowledged that PPD is distinct from PPP during the June 18, 2008 interview, but was concerned about the language of the claims. Thus it would appear any issue relating to Stowe, which discusses PPD, was resolved during the interview. Yet Stowe was cited again, without any explanation, in Examiner Jagoe's first Office Action mailed September 30, 2008. In response to Appellant's query about Stowe in the Response mailed January 28, 2009, Examiner Jagoe recited the passage from Examiner Packard's May 28, 2008 Office Action, *i.e.*, "Stowe was simply used to show the postpartum patient population may include those without predisposed depression tendencies"

(*see* May 19, 2009 Office Action, page 18). As explained above, Appellants *have never argued* otherwise.

Finally, the Examiner has asserted that Stowe is improperly attacked individually. Stowe is attacked in the sense that Appellants maintain its irrelevance. Obviousness rejections are commonly based on more than one reference, and while the teaching of the art must be considered in its entirety, at some point, each reference must be considered independently for what it teaches. Appellants merely seek to understand what, if anything, Stowe is being cited for.

Stowe discusses PPD, which is distinct from PPP. As explained on page 18 of the October 28, 2009 Appeal Brief, *neither Stowe nor Schatzberg* suggest that PPP is related to glucocorticoid regulatory dysfunction. The proposed teaching of Stowe, that the postpartum patient population may include those without predisposed depression tendencies, is completely irrelevant to the issue presented to the Board.

It is irrelevant because Stowe, alone or in combination with Schatzberg, Bradley, or Gebhard, fails to teach or suggest that PPP is related to glucocorticoid regulatory dysfunction.

3. Exhibits distinguishing PPP from other postpartum psychiatric disorders were submitted for further description of PPP

For the first time, the Examiner states that the significance of exhibits distinguishing PPP from other postpartum psychiatric disorders is unclear (Examiner's Answer, bottom of page 16).

Appellants maintain that PPP is a rare phenomenon, and, at the time of the invention, the etiology of PPP was not understood. A number of exhibits have been submitted to support this point.

Assuming that the Examiner is referring to Exhibits B– E (submitted with the Appeal Brief mailed October 28, 2009), they were originally submitted to provide some context of how PPP was understood by those of skill. These exhibits do distinguish PPP from other postpartum psychiatric disorders, and indeed, they were initially filed with the Response mailed February 13, 2008, in part to distinguish PPP from PPD. However, Exhibits B– E also show that

PPP is a rare disorder, and that its etiology was not well-understood at the time of the invention. For example, Exhibit C includes the following discussion of PPP that indicates uncertainty in the field:

> ported. Although most believe that this illness is indistinguishable from an affective (or manic) psychosis, some have argued that puerperal psychosis may be clinically distinct in that it is more commonly associated with confusion and delirium than nonpuerperal psychotic mood disorder.

The following passage from Exhibit E also shows that the cause of PPP was unknown:

> Psychiatrists aren't sure what causes such a sudden and powerful break with reality, but they believe the changing hormones and stress of childbirth are somehow involved.

Appellants submit that, without objective evidence that PPP was known to be associated with glucocorticoid regulatory dysfunction, the *prima facie* case cannot stand. The above references disclose that PPP was of unknown etiology at the time of the invention.

4. The art teaches away from treating a postpartum mother with a GRA

Appellants maintain that one of skill at the time of the invention would not have a reasonable expectation of success in treating PPP with a GRA, in part because the art teaches away from doing so. Appellants have submitted references on this point, *i.e.* Exhibits F and G (submitted with the Appeal Brief mailed October 28, 2009). These exhibits disclose that cortisol levels fall after childbirth. One would not expect to successfully treat a new mother, who presumably has reduced cortisol levels, with an agent that inhibits glucocorticoid signaling.

For the first time, the Examiner argues that Exhibits F and G teach that cortisol is only reduced immediately postpartum, and that the claims are drawn to treatment within 9 months of childbirth (Examiner's Answer, bottom of page 17). According to the Examiner, the evidence relied upon for teaching away is not recited in the claims.

For the sake of accuracy, Appellants note that the claims recite that the first psychotic symptoms arise within nine months of childbirth, not that treatment occurs within the first nine months.

Exhibits F and G do not provide a precise timeline for postpartum cortisol levels and presumably this varies from individual to individual. It is therefore unclear what to incorporate into the claim, were Appellants to comply with the Examiner's suggestion. Do cortisol levels return to pre-pregnancy levels one day later, three weeks later, a few months later? Is it the same for every woman?

Appellants dispute that the Examiner has made a *prima facie* case of obviousness, because there is no evidence on the record that one of skill at the time of the invention would have expected PPP to be related to glucocorticoid regulatory dysfunction. Despite the lack of a *prima facie* case, Appellants provided evidence that one of skill would not treat a new mother with a GRA. Presumably, her cortisol levels would be low in the postnatal period, and administration of a GRA would not be appropriate.

Moreover, as explained below, fluctuating cortisol levels during the postpartum period may not be an important factor in the etiology of PPP.

The inventor, Dr. Belanoff, has developed a theory based on epidemiological information gathered from a survey of individuals suffering from various psychiatric conditions. Statistical review of conditions having a psychotic element reveals a genetic predisposition to cortisol sensitivity in a small percentage of the population. That is, for certain conditions, a small percentage of individuals will exhibit psychotic symptoms in response to slightly stressful conditions. Note that cortisol is known as the stress hormone.

Appellants' evidence about falling postpartum cortisol levels was not considered until the Appeal stage, so Appellants are only now presenting one of Dr. Belanoff's theories underlying the present invention. Dr. Belanoff believes that a small percentage of us are particularly sensitive to cortisol, so that even if cortisol levels are within the normal range, a sensitive individual will experience an extreme, perhaps psychotic, reaction.

PMD, as disclosed in Schatzberg, provides an example of this phenomenon. PMD only arises in a small percentage of depressed patients. The data provided in Schatzberg demonstrates that this population can be successfully treated with a GRA.

Childbirth can also be described as a stressful experience. Yet only a small percentage of women experience psychotic symptoms after birth, in the range of 1% (*see*

Exhibits B- E). Dr. Belanoff concluded that the psychotic symptoms of PPP may result from cortisol sensitivity.

For this sensitive population, the exact timing of when cortisol levels fall and return to normal after birth may not be the decisive factor in developing PPP. The stress of handling a new baby is sufficient to trigger psychotic symptoms. The Examiner's Answer regarding Exhibits F and G does not consider the possibility of a cortisol sensitive population.

Despite the lack of a *prima facie* case of obviousness, Appellants have met the burden of refuting alleged obviousness with evidence teaching away from treating a postpartum mother with a GRA. In addition, the small population of mothers that experience psychotic symptoms after childbirth may be responding to only slightly elevated or normal cortisol levels.

In conclusion, Appellants maintain that the Examiner has yet to establish that one of skill would reasonably expect to successfully treat PPP with a GRA. The Examiner has not shown that PPP is related to glucocorticoid regulatory dysfunction. The art teaches that cortisol levels fall after birth, thus teaching away from treating a postpartum mother with a GRA. Appellants respectfully request withdrawal of the rejections under 35 USC § 103.

B. GROUND OF REJECTION 2 (Claims 3 and 4): 35 USC § 112, first paragraph

The Examiner has maintained the written description rejection of claims 3 and 4, again asserting that the following terms are ambiguous:

- Steroidal skeleton
- At least one
- Phenyl containing moiety
- Dimethylaminophenyl moiety (Examiner's Answer, page 19).

Appellants have addressed this issue, and submitted evidence that the terms were common in the art as early as the 1970s (January 28, 2009 Response, pages 5-6, and October 28, 2009 Brief, pages 24-25). Given the familiarity of the terms and the examples of the compounds

disclosed in the specification, one of skill would "immediately envisage" the compounds described in claims 3 and 4.

1. The compounds recited in claims 3 and 4 are not the "point of novelty" of the claimed methods

The Examiner's Answer does not address the "point of novelty" argument set forth on pages 22-23 of the October 28, 2009 Brief. This is the argument that, unless the claimed element is the point of novelty, the claims need not recite detailed structural features. For the present claims, Appellants maintain that while one of skill would immediately envision the compounds recited in claims 3 and 4, this is more than is required for the recited compounds. The point of novelty of claims 3 and 4 lies in the inventor's insight that a GRA could be used to treat PPP, not in the particular GRA that is used to do so.

As explained in the Brief, a claim can validly recite a class of compounds defined primarily by a shared function (in this case, GRAs) in the following circumstances:

(i) when the point of novelty of the claim does not reside in the compounds themselves,

(ii) the class of compounds is known, and readily detectable by a routine assay, and

(iii) there are a number of compounds that can be successfully used.

The compounds recited in claims 3 and 4 fall into all three categories. The point of novelty lies with treating PPP with a GRA, not with the particular GRA. Steroidal GRAs with an 11-β phenyl-containing moiety represent a known class of GRAs (*see* pages 10-12 of the specification). The activity of a compound to inhibit glucocorticoid receptor can be tested using routine assays (*see* pages 14-16 of the specification). A number of compounds can be successfully used (*see* pages 10-12 of the specification).

There is a difference in the amount of written description required for a recited compound if it is used in a novel method than if the compound itself is claimed. This is supported by the Written Description Training Materials (Rev. 1, March 25, 2008), published by the USPTO. Example 16 outlines the written description analysis of a "Process Claim Where Novelty Resides in the Process Steps."

The claim in Example 16 is directed to a method of introducing a nucleic acid into the mitochondria of a mammalian cell. The insight disclosed in the specification is that compound X is useful for introducing nucleic acids into mitochondria under specific conditions. The claimed method is described as useful for treating diseases caused by mutations in mitochondrial DNA. The specification does not disclose the structure of commonly mutated mitochondrial genes, but provides an example using a beta-galactosidase gene as the nucleic acid.

The Conclusion of Example 16 is that the claim meets the written description requirement.

Example 16 is analogous to the present situation. Here, the inventor's insight is that GRAs are useful for treating PPP. The present specification does not disclose every GRA with at least one phenyl-containing moiety at the 11-β position of the steroidal skeleton, but does provide specific examples of such compounds and citations to publications about the compounds. The specification in Example 16 does not disclose the structure of any mitochondrial genes, yet the recited "nucleic acid" is considered sufficiently described.

The specific GRAs recited in claims 3 and 4 are not the point of novelty of those claims, thus, the disclosure relating to GRA with at least one phenyl-containing moiety at the 11-β position of the steroidal skeleton is sufficient to meet the written description requirement.

2. The legal standard applied by the Examiner is unclear

A minor additional issue was raised by the Examiner's Answer, relating to the standard for written description that is being applied. In an effort to better understand the rejection, Appellants questioned the standard applied by the Examiner, as it seemed to be closer to that for enablement, *i.e.*, the Examiner asserted that the invention "would require undue, unpredictable experimentation" (October 28, 2009 Appeal Brief, page 26). In response, the Examiner states that she cannot find these words in the rejection (Examiner's Answer, page 20). Appellants point to page 14 of the May 19, 2009 Final Rejection:

"part of a molecule". It is still unclear what the other part (or half) of the moiety or part of the molecule is, so one is left to theorize and conjecture about the structure of the molecule. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention in the method of ameliorating the psychotic symptoms of a post-partum patient comprising the step of administering a GRA with a steroidal skeleton with "at least one phenyl containing moiety in the 11-β position" or "at least one dimethylaminophenyl moiety in the 11-β position". Applicant states that mifepristone is

This issue does not change Appellant's position, but further illustrates a lack of careful application of the law.

To comply with the written description requirement, the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Given that the terms recited in claims 3 and 4 are well-known in the art, and that the specification describes examples of such compounds, Appellants submit that the present specification meets the requirement.

CONCLUSION

For these reasons, it is respectfully submitted that the rejections under 35 USC § 103 and under the first paragraph of 35 USC § 112 for written description should be reversed.

Respectfully submitted,

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CLAIMS APPENDIX

1. A method of ameliorating the psychotic symptoms of a patient having postpartum psychosis, comprising administering an amount of a glucocorticoid receptor antagonist effective to ameliorate the psychotic symptoms of the postpartum psychosis, with the proviso that the first psychotic symptoms arise within nine months of childbirth, that the patient has never suffered any psychotic condition not triggered by childbirth, and that the patient did not suffer from psychosis prior to parturition.

2. The method of claim 1, wherein the first psychotic symptoms arise within eight weeks of childbirth.

3. The method of claim 1, wherein the glucocorticoid receptor antagonist comprises a steroidal skeleton with at least one phenyl-containing moiety in the 11-β position of the steroidal skeleton.

4. The method of claim 3, wherein the phenyl-containing moiety in the 11-β position of the steroidal skeleton is a dimethylaminophenyl moiety.

5. The method of claim 4, wherein the glucocorticoid receptor antagonist comprises mifepristone.

6. The method of claim 4, wherein the glucocorticoid receptor antagonist is selected from the group consisting of 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9 estradien-3-one and 17β-hydroxy-17α-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.

7. The method of claim 1 wherein the glucocorticoid receptor antagonist is selected from the group consisting 4α(S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol and 4α(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol.

8. The method of claim 1, wherein the glucocorticoid receptor antagonist is (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

9. The method of claim 1, wherein the administration is once per day.

10. The method of claim 1, wherein the mode of administration is oral.

11. The method of claim 1, wherein the mode of administration is by a transdermal application, by a nebulized suspension, or by an aerosol spray.

15. The method of claim 1, wherein the glucocorticoid receptor antagonist is a specific glucocorticoid receptor antagonist.